GAS WHAT?

Policy Questions on Medical Gases

Reprinted from: Human Drug CGMP Notes
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Human Drug CGMP Notes (June 1997)

1) What is the current policy on gas product yield reconciliation? I understand the Compressed Gas Association filed a citizens petition requesting exemption from this requirement.

Reference: 21 CFR 211.103, Calculation of yield; 211.184(c), Component, drug product container, closure, and labeling records.

The Compressed Gas Association filed a citizens petition requesting that medical gases be exempt from the requirements for yield reconciliation. On May 11, 1995, the agency concurred with the CGA based on the amounts of product loss through evaporation from storage tanks, large cryogenic dewars, the filling operations, and the filling of large amounts of industrial product from the same storage tanks.

The agency will publish a notice in the Federal Register proposing to amend the CGMP regulations accordingly. The notice will include an interim enforcement policy that will apply the exemption. However, existing requirements remain in effect until the notice is published.

2) Must batch production records for compressed medical gases contain copies or specimens of all labeling used, or are alternative measures acceptable? What regulatory follow up would be appropriate if labeling/copies are required but lacking?

Reference: 21 CFR 211.188(b)(8), Batch production and control records.

Batch production records for compressed medical gases must contain copies or specimens of all labeling used, per 21 CFR 211.188(b)(8). Photographs or photocopies of large labeling that would be awkward to physically append to the records may be used in place of original labeling. It's important to have labeling, or accurate copies thereof, to enable investigations and problem resolution in the event of mix ups. Although additional labeling controls may contribute to preventing mix-ups, such controls are not substitutes for including labeling specimens or copies in the batch

records.

Accordingly, it would be appropriate to include in an FDA 483 the observation that batch production records lacked copies or specimens of all labeling used. The appropriateness of pursuing further actions, such as issuance of warning letters, would have to be assessed in the context of all inspection findings, the potential public health risks and the firm's compliance history.

Human Drug CGMP Notes (March 1997)

1) What is SPORTS OXYGEN? Is it possible to import SPORTS OXYGEN into the U.S.?

Reference: Import Alert 66-37

SPORTS OXYGEN is a small pocket-sized, personal use oxygen system, which has been imported from Japan. The product promises athletic enhancement and makes other drug claims. Because these products are incapable of supplying an oxygen flow rate of at least six (6) liters of Oxygen U.S.P. per minute for at least 15 minutes, they are regarded as new drugs. Without approved NDAs they are not legal for importation into the U.S.

2) Is the February, 1989, Compressed Medical Gases guideline FDA's current guidance for the medical gases industry?

Yes. However, the February guideline is out of print and in need of updating. We are in the process of revising and re-issuing that guidance document.

For an idea of how the guidance document will be revised, see the December 4 version of "Fresh Air '96," presented during the Cincinnati District Office medical gases workshop. For a copy of "Fresh Air '96" contact this office either by phone or e-mail.

Human Drug CGMP Notes (December 1996)

1) Has FDA modified the federal caution statement requirement for medical oxygen?

Reference: Section 503(b)(4) of the Food Drug and Cosmetic Act; 21 CFR Sections 201(b)(1) and 211.130.

Yes, On September 19, 1996, FDA informed the Compressed Gas Association that a final decision had been reached on its citizen petition. The label for medical oxygen should bear the statement, "For emergency use only when administered by properly trained personnel for oxygen deficiency and resuscitation. For all other medical

applications, Caution: Federal law prohibits dispensing without prescription."

A firm may meet this requirement by applying an additional sticker to the label which contains the above statement, until new labels are ordered.

2) What are FDA requirements for opening an oxygen spa bar in the U.S.? Can industrial grade oxygen or oxygen concentrators be substituted for medical oxygen in such use?

Reference: Section 503(b)(1)(B) of the Food Drug and Cosmetic Act

Oxygen spa bars have been around in Japan for many years, and are starting to show up in Canada. These establishments don't administer oxygen for medical or emergency use in the traditional sense. We have received inquiries as to FDA'S requirements regarding this type of operation. This is a very interesting business concept; however, medical oxygen is defined as a prescription drug which requires a prescription in order to be dispensed, except as described above, for emergency use.

Oxygen spa bars advertising that makes unproven medical claims, e.g. a skin care treatment, anti-aging, hangovers, fatigue, migraine headaches, etc. would render the oxygen a new drug.

Further, we would strongly discourage the use of industrial grade oxygen due to the lack of control exercised over industrial high pressure cylinders and the possibility of contamination occurring. As for the use of oxygen concentrators, these are prescription devices and as such would require a prescription.

Human Drug CGMP Notes (September 1996)

1) Are scuba diving tanks of air regulated as medical gases?

Reference: Federal Food Drug and Cosmetic Act, Section 201(g), Definitions

No. Scuba diving tanks hold compressed breathing air, which is not a medical gas, but is, along with fittings and the regulator, regulated by the Consumer Product Safety Commission (CPSC). Empty tanks are regulated by the Department of Transportation which addresses cylinder
specifications and hydrostatic testing.

You should forward any complaints you receive regarding scuba tanks to the CPSC, Office of Compliance, 4330 East West Highway, Room 613.11, Bethesda, MD 20814. The CPSC general phone number is 301-504-2706 or 301-504-0580.

Human Drug CGMP Notes (June 1996)

1) Is the use of a stainless steel sampling cylinder, more commonly known as the hoke bomb, acceptable for the testing of a storage tank?

Reference: 21 CFR 211.84(d)(2) Testing and approval or rejection of components, drug product containers, and closures; and 211.165(d) Testing and release for distribution.

Yes, provided the firm has validated the process. A hoke bomb is a stainless steel cylinder with a valve on each end which allows a gaseous product to flow through. The most significant step in the validation process is the time required to fully purge the cylinder which provides assurance that complete evacuation of the cylinder has been accomplished.

2) What are the CGMP requirements for equipment used for industrial grade products and then used for medical products?

Reference: 21 CFR 211.67(a, b, & c) Equipment cleaning and maintenance, 211.100(a) Written Procedures; and 211.25(a) Training Equipment, i.e., hoses, temporary vessels, etc. used in the delivery of a medical drug product is considered an integral part of the drug delivery system and as such is a regulated under the drug CGMPs.

Any equipment used for medical use is required to be cleaned, maintained, and sanitized at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official requirements in the delivery of a medical product.

Detailed written procedures should be established, and records maintained of the cleaning, sanitizing, and inspection. Another vital CGMP requirement is the assurance that all personnel involved with the equipment on the medical side are adequately trained to perform their designated function.

Problems arise from the contaminants that may be introduced while being used for industrial grade products. Equipment used for industrial products must be qualified prior to being used for medical product, i.e., should be tested for any contaminant that the equipment may have come in contact with, before a medical drug product is introduced.

Human Drug CGMP Notes (March 1996)

1) May a firm use industrial grade nitrogen as a blanketing agent during the manufacturing of a drug product?

Reference: 21 CFR 211.110(a) and(c), Sampling and testing of in-process materials

and drug products; 211.165(a), Testing and release for distribution.

Unless the industrial grade product is analyzed for all possible impurities and contaminants, it would be unacceptable to use industrial grade products in the manufacturing of pharmaceutical drugs.

The filling of medical and industrial grade nitrogen whether it be gaseous or liquid is quite unique. The problems we have seen are usually not with the product itself, but rather with the container closure system, i.e., the high pressure cylinder and hazardous substances to which they have been exposed.

Industrial cylinders are widely distributed throughout all types of industry, and are routinely exposed to hazardous substances, some of which are extremely toxic, i.e., hydrocarbons, arsenic compounds, chlorine, etc. Therefore, it would be nearly impossible to determine what a specific cylinder had been exposed to and to analyze for that specific contaminant.

On the other hand, medical gas cylinders are prepared under carefully controlled conditions to ensure that the drug product meets the requirements of both FDA and the U.S.P., and are not exposed to contamination from industrial sources. Each high pressure cylinder undergoes rigorous pre-qualifying inspections and examinations with one of the most significant being the vacuum evacuation step, prior to filling a product.

According to USP23, the General Notices, Tests and Assays, Foreign Substances and Impurities, it is impossible to include in each monograph a test for every impurity, contaminant, or adulterant that might be present. Tests suitable for detecting such occurrences should be employed in addition to the tests provided in the individual monograph.

Refer to the June 1995 HUMAN DRUG CGMP NOTES for nitrogen produced via pressure swing adsorption and cryogenic nitrogen.

2) Is it acceptable for the owner of a vessel to apply a small sticker to denote its ownership, even though the vessel is filled by a different firm that is identified in the vessel's labeling?

Reference: 21 CFR 211.130, Packaging and labeling operations, 201.1, Drugs; name and place of business of manufacturer, packer, or distributor.

Yes, a firm may place a small sticker, commonly referred to as a possession/ownership sticker, on a vessel as long as the sticker does not obstruct required labeling. In addition, the sticker must not be misleading. For example, it should be qualified by a statement such as, "This empty vessel or this vessel when empty is the property of, or belongs to, `Firm X, address, and telephone number.'"

Human Drug CGMP Notes (December 1995)

1) What are the requirements for modifying the zero step of the calibration procedure for Servomex (R) oxygen analyzers?

Reference: 21 CFR 211.160(b)(4) (General requirements); and 211.165(e) (Testing and release for distribution); Subpart I (Laboratory Controls)

The Servomex (R) Oxygen Analyzer instruction manual states that the analyzer zero step (zeroing) is to be checked once a week, after transportation, or if the instrument has undergone a temperature change of 10 degrees C/18 degrees F or more.

It has been our experience that these instruments are usually placed in a room that is well ventilated, and in many instances open to the outside environment when filling operations are underway. Thus, the analyzer would be expected to be exposed to temperature fluctuations of 10 degrees C/18 degrees F or more during a 24 hour period.

Calibration of the analyzer zero step at weekly intervals may be appropriate if a manufacturer can document that the instrument had not been moved and that the temperature of the area where the analyzer is kept did not fluctuate more than 10 degrees C/18 degrees F. The use and retention of 24 hour temperature recording charts would be acceptable documentation.

If a manufacturer is unable to supply such documentation, we will continue to consider it a major CGMP violation if the analyzer is not calibrated daily, or more often, when cylinders of Oxygen U.S.P. are being filled.

Additionally, before we would even consider accepting monthly calibration of the analyzer zero step, we would require validation data to support a firm's contention that monthly calibration is appropriate. Such data should include 24 hour temperature charts and daily zero step calibration checks for at least one (1) year.

Please note that each individual facility would be required to perform its own oxygen analyzer validation study.

2) Are the new digital readout Servomex(R) 244 oxygen analyzers acceptable for oxygen analysis?

Reference: 21 CFR 211.165(e) (Testing and release for distribution)

FDA does not approve or disapprove laboratory instrumentation. However, we are aware that the manufacturer of Servomex (R) analyzers has instituted a major modification to the Servomex 244 oxygen analyzer (OA) that merits further validation

before it can be acceptable.

The firm implemented several internal changes and converted the analyzer from an analog to a digital readout but did not validate U.S.P. methodology equivalency.

Servomex(R) is developing validation data and is expected to send it to us upon completion. In the meantime, absent data that demonstrate U.S.P. equivalency, the 244 OA with a digital readout would not be acceptable for the analysis of medical gases, especially Oxygen U.S.P.

Firms which use the digital 244 oxygen analyzer are required under the above reference to demonstrate U.S.P. method equivalency.

Nevertheless, the analog 244 OA remains an acceptable analyzer, when used in conformance with applicable CGMP requirements, for analysis of medical oxygen.

Human Drug CGMP Notes (September 1995)

1) What are the requirements for the calibration of vacuum gauges?

Reference: 21 CFR 211.68 (Automatic, mechanical, and electronic equipment).

Vacuum gauges used during the evacuation of high pressure cylinders require a daily "calibration." This simple calibration consists of an inspection of the gauge prior to the pulling of a vacuum, and with no pressure on the line. The needle should return to "zero"; if not, then an adjustment is required. If the needle cannot be adjusted and returned to zero, then the gauge should be replaced.

In addition, a firm is required to establish written calibration procedures describing their process and should document that the calibration was performed.

2) What are the labeling requirements for cryogenic home vessels?

Reference: 21 CFR 211.130(a) (Packaging and Labeling Operations)

According to 211.130(a), a firm should establish written procedures designed to assure that correct labels are used for its drug products. Until FDA's labeling requirements have been finalized, both high pressure cylinders and cryogenic home vessels are required to have adequate
labeling. At the current time, we are requiring cryogenic home vessels to bear labeling similar to that applied to high pressure cylinders, but for the liquid phase. This includes bearing the statement, "Caution: Federal law prohibits dispensing without prescription"

in accordance with
21 CFR Section 201.100(b)(1).

Please note that this requirement pertains to oxygen used for therapy, and not emergency use. So, a firm should determine when the oxygen is intended for emergency use.

Human Drug CGMP Notes (June 1995)

1) What is pressure swing adsorption (PSA) and what are the requirements for the nitrogen produced by PSA, if the product is used during the manufacture of a drug product, such as tablets, capsules, etc.?

Reference: 21 CFR Sec. 211.110(a & c), Sampling and testing of in-process materials and drug products.

We have received numerous inquiries regarding the use of PSA in the manufacture of pharmaceutical drug products, where the nitrogen will be used as a blanketing agent, etc.

The principle of PSA is where a stream of air is compressed, filtered, and then passed through a molecular sieve which selectively adsorbs oxygen, leaving the remaining process gas stream nitrogen rich. Some units are capable of producing flow rates up to 100,000+ scfh and purity
levels as high as 99.9995% with purification.

If a firm is using PSA, then it should establish control procedures to monitor the output and to validate the performance of those manufacturing processes that may cause variability in the
characteristics of in-process material and the drug product. This would also pertain to nitrogen received in large cryogenic vessels, i.e., tube trailers, storage tanks, etc.

2) What's the current policy regarding the filling of a vacationing patient's vessel, either high pressure cylinder or cryogenic home vessel?

Reference: 21 CFR Sec. 211.84, Testing and approval or rejection of containers and closures; 21 CFR Sec. 211.94(c), Drug product containers and closures; 21 CFR Sec. 211.165(a), Testing and release for distribution.

This type of scenario, which is similar to the filling of a cryogenic vessel at a patient's home, is considered an emergency need for the drug product. If a patient is on vacation and/or traveling away from his/her residence, and encounters a need for oxygen, then a firm would be allowed to fill the patient's vessel without performing all

the required testing or all the required prefill inspections, provided 1) the firm receives a prescription, 2) the patient remains at the firm, i.e.,
cannot leave the premises, 3) the employee who receives the vessel performs the filling and returns it promptly to the patient, 4) the incoming drug product has been tested and meets all specifications, and 5) the minimum visual inspections are performed, i.e., valve and external examination, labeling, coloring, correct valve, etc. Finally, the firm should obtain the patient's final destination including an address and a telephone number, in case of a recall.

Human Drug CGMP Notes (March 1995)

1) What is the significance of the air liquefaction statement? Is further testing required if this statement is not available?

Reference: 21 CFR 211.165(f), Testing and release for distribution.

The United States Pharmacopeia XXIII Oxygen monograph states that if the air liquefaction statement is present then a firm is exempt from performing the carbon dioxide and carbon monoxide impurities testing.

Let's look at it another way; there are four (4) required tests listed under the oxygen monograph. They are the identification test, the carbon dioxide impurity test, the carbon monoxide impurity test and the assay. As long as the air liquefaction statement is available either by a letter from the supplier or by a certificate of analysis, then the identification and the assay are the only tests required.

2) Has the odor test been eliminated from the prefill inspections, due to concerns over pathogenic contamination or other dangerous compounds?

Reference: 21 CFR 211.84(d)(3), Testing and approval or rejection of components, drug product containers, and closures; 211.94(b&c), Drug product containers and closures; and, 211.113(a), Controls of microbiological contamination.

No. The Compressed Medical Gases guideline, page 5 and 6, states that since the containers and closures for medical gases are reused over and over again, they require special considerations, i.e., inspections, prior to filling. Therefore, an odor test of each cylinder to detect foreign odors is required. Of course, the odor test should not be performed on anesthetic gases such as nitrous oxide, or on carbon dioxide.

At the present time, we are unaware of any problems and have received no reports of medical gases becoming contaminated with pathogens. However, if this is a problem or a major concern, then a medical gas manufacturer would be required in accordance with 21 CFR 211.113, Control of Microbiological Contamination, to establish written procedures designed to prevent

objectionable microorganisms in the drug product.

Human Drug CGMP Notes (December 1994)

1) What are the requirements for standard reference gases that are to be used in the calibration of oxygen analyzers?

Reference: 21 CFR 211.194(c), Laboratory Records

All calibration gases should be purchased from a specialty gas manufacturer and backed up by a certificate of analysis (COA). Note - this COA is not required to provide the air liquefaction statement, since the calibration gases are not medical products.

Recent problems encountered at several filling firms supplying standard reference gas has prompted a change in policy. The problems observed ranged from inadequate testing, inadequate calibration of the analyzers, to inadequate calibration standards.

2) What training is acceptable for the filling of medical gases?

Reference: 21 CFR 211.25(a), Personnel Qualifications

This is one of the most neglected CGMP violations noted in the industry today. While it is acceptable for a firm to provide on-the-job training, the individual(s) responsible for providing this training should be knowledgeable either through education, training, or experience. We expect the on-the-job training to be provided at frequent intervals. Likewise, it is important that CGMP training be conducted by qualified individuals on a continuing basis and with sufficient frequency to ensure that employees remain familiar with the CGMP requirements.

This training should be addressed in sufficient detail in the firm's training protocol or procedures, and should be documented.

Human Drug CGMP Notes (September 1994)

1) Is the Pressure Differential Method an acceptable, alternate method for the testing of nitrous oxide?

Reference: 21 CFR 211.165(e) Testing and release for distribution.

Yes, this is an acceptable testing methodology for the determination of strength/potency of nitrous oxide. However, an identification test must be performed concurrently to preclude
the presence of carbon dioxide which will provide the same results as nitrous oxide.

2) Are check valves, i.e., double block and bleed, acceptable and effective at preventing contamination of the incoming product?

Reference: 21 CFR 211.110(a), Sampling and testing of in-process materials and drug products

Check valves should not be used in the manufacture of medical gases, unless a validation study has been performed.

A recent FDA inspection found a large firm utilizing several check valves which are designed to prevent the back flow of a gas back into a supply line. According to the valve manufacturer, these valves are maintenance free. Realizing that these valves are mechanical, the investigator did not believe this claim and requested the firm's validation study proving that these valves function as required. The firm did not have a study and proceeded to perform a validation of these valves to demonstrate their acceptability. Consequently, the firm's validation study showed that these valves were malfunctioning, and could allow a foreign gas to contaminate (back flow) the incoming supply lines.

Human Drug CGMP Notes (June 1994)

1) Is it acceptable for a medical gas filler to assign a single lot/batch number for the entire day's production?

Reference: 21 CFR 211.130(b), Packaging and labeling operations

No. A manufacturing operation, such as the filling of high pressure cylinders on a multi-outlet manifold, is governed by a set of manufacturing procedures or conditions which when performed from the beginning to the end of a process provides assurance that the batch is uniform and consistent. Further, each batch is in itself a separate entity with little resemblance to the previous batch other than the use of the same incoming materials with subsequent batches exhibiting their own uniqueness. According to the CGMP, each manifold filling sequence, each uninterrupted filling sequence, each cryogenic vessel filled, and each storage tank filled is considered a new batch and is required to be assigned a new lot/batch number.

This does not apply to cryogenic home vessels filled at a patient's home.

2) What is the accuracy of the U.S.P. methodology for the analysis of Oxygen U.S.P.? What oxygen analyzers are acceptable?

Reference: 21 CFR 211.165(e), Testing and release for distribution; 211.194(a)(2), Laboratory records; and, Compressed Medical Gases Guideline, Rev. 2/89.

The accuracy of the U.S.P. method, the Orsat burette is plus or minus 0.1%. Analytical equipment accuracy is required to be equivalent to or greater than this value.

Analyzers that operate on the paramagnetic susceptibility principle, and have the above accuracy would be considered acceptable. Some of the oxygen analyzers commonly encountered and found to be acceptable are the Servomex 570A and the 244OA - upper scale only; Western
Enterprise's TR104 and MADA Medical's OAP640 (These two are actually Servomex 570A); Rosemount Analytical and Siemen. Paramagnetic analyzers provide both a strength/potency and an identification test in one result.

Handheld analyzers operating on the fuel cell, electrochemical cell, polarographic cell or the galvanic cell, such as the Hudson RCI, Catalyst Research's MiniOx, etc. are capable of providing a specific oxygen identification test result only. These analyzers have an accuracy between plus or minus 1% to 3%.